Limitations of the use of spectral analysis of heart rate variability for the estimation of cardiac sympathetic activity in heart failure

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Spectral analysis of heart rate variability has gained popularity as a simple, non-invasive tool for assessing autonomic function in both normal subjects and in patients in a variety of clinical settings. However, the use of this method as a means of estimating the magnitude of cardiac sympathetic activation in individual patients with heart failure has proved disappointing, with a lack of concordance with more direct measures of sympathetic outflow. This review will describe the rationale involved in using sympathetic indices obtained from spectral analysis of heart rate variability to assess cardiac sympathetic outflow in normal subjects and patients with heart failure. The specific limitations and technological concerns that dictate how it may most effectively be used in this patient population will be discussed.

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Introduction

Power spectral analysis of heart rate variability has the advantage of being a simple, non-invasive measurement capable of assessing dynamic changes in the autonomic control of heart rate\(^1\). Briefly, it uses frequency domain analysis to identify superimposed oscillations which contribute to variations in heart rate. Since the sino-atrial node is under the control of the autonomic nervous system, it is thought that the study of this oscillatory behaviour may identify autonomic inputs to the heart.

A variety of methodology has been used in the past. This limits the ability to compare studies and, as a result, an attempt has been made by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology to standardize methods\(^4\). However, this effort, to which the reader is directed, is yet to have substantial impact. Most commonly used are the fast Fourier transform and the autoregressive methods. Although the former has been shown to be reliable\(^5\), it may have a technical limitation in that an underlying periodicity in the data is assumed, whereas the heart rate variability signal is a pseudorandom phenomenon\(^1\).

Another method, known as coarse-graining spectral analysis, is now used by several investigators\(^6,7\), including ourselves\(^8\). The underlying concept is that harmonic contributions to heart rate variability are superimposed on broadband non-harmonic ‘noise’. This occurs primarily in the very low frequency range, from 0.00003 to 0.1 Hz\(^6\), is fractal in nature\(^11\), and can be quantified by plotting the log of spectral power as a function of the log of frequency (a 1/f\(^B\) plot). Since non-harmonic noise can be a confounding influence within the low frequency range, this method provides more precise estimates of the harmonic contributions to low and high frequency power\(^6,7\). This feature may be particularly useful in conditions characterized by...
diminished spectral power in the low frequency range, such as heart failure[12–14].

Both decreased heart rate variability[15–17] and sympathetic nervous system activation[19] are independent risk factors for decreased survival in heart failure. However, in contrast to more direct measures of sympathetic activation, such as cardiac and total body noradrenaline spillover and skeletal muscle nerve microneurography[19–25], spectral indices of sympathetic modulation (absolute or normalized low frequency power) are not significantly increased in patients with heart failure[8,10]. Indeed, in many patients with end-stage heart failure, heart rate becomes invariable, and refractory to analysis by conventional spectral techniques. This has resulted in some scepticism when considering changes in heart rate variability spectral power as indicators of sympathetic outflow to the heart in this patient population[10,26–28], and leads to the question of how it may be effectively employed in patients with heart failure.

Thus, this review will: (1) describe the validation of heart rate variability as a method for assessing cardiac autonomic function in animal models and subjects with normal ventricular function; (2) consider why this methodology may be clinically important in patients with heart failure while identifying relevant limitations; (3) review the time course of changes in heart rate variability in both experimental and human heart failure; (4) outline the changes in heart rate variability that occur in patients with heart failure, possible mechanisms and related technological challenges; and (5) survey interventions which may have a positive impact on heart rate variability in patients with heart failure.

Heart rate variability in normal animals and humans

The rationale for identifying high frequency power (>0.15 Hz) as an indicator of parasympathetic activity came largely from pharmacological studies in both animals and humans. Administration of atropine or other parasympathetic blocking agents virtually abolished the high frequency component of heart rate variability[2,3,29].

Interpretation of the absolute or normalized low frequency (0.05–0.15 Hz) component of spectral power as an indicator of sympathetic activity resulted from similar animal work. In dogs, an increase in low frequency power was observed during baroreceptor unloading with nitroglycerin and was prevented by prior bilateral stellectomy[1,29]. In decerebrate cats, both increased impulse activity of cardiac sympathetic nerves and reflex sympathetic excitation induced an increase in low frequency power, with a concurrent reduction in high frequency power[30]. The opposite occurred in response to reflex sympathetic inhibition[30].

Further support for this concept was supplied by human studies which showed increases in absolute or normalized low frequency spectral power with various manoeuvres known to increase central sympathetic outflow, such as standing[2], tilt[2,17], exercise[15] and lower body negative pressure[7,32], or which decrease sympathetic nerve traffic, such as sleep or clonidine[33], or after beta blockade with propranolol[2]. This association is not straightforward, however, since low frequency spectral power contains much vagal influence[2,3,34]. Therefore, the ratio between low and high frequency power has been proposed as an estimate of the balance between these two opposing neural mechanisms, and often termed ‘sympathovagal balance’[1]. Although this ratio is often used to represent cardiac sympathetic activity[1,35], this concept remains controversial[34,36].

Increasing sympathetic outflow with nitroprusside does affect the spectral components of muscle sympathetic nerve activity (MSNA) variability, such that an increase in the absolute levels of MSNA, as measured by microneurography, is associated with a shift towards low frequency spectral power[37]. The authors of this study also described synchronous changes in low and high frequency oscillations in both heart rate and MSNA variability during interventions designed to raise and lower sympathetic outflow in normal subjects, and suggested a shared central mechanism of control for sympathetic and parasympathetic modulation[37].

The common theme in all of these validation studies is that their conclusions arise not from between-subject comparisons, but from within animal or human comparisons, whether obtained under resting conditions, or in response to interventions. Indeed, the limited number of studies which examine between subject comparisons of heart rate variability spectra suggest that this measure is not sensitive enough to detect, in healthy individuals, well-described differences in autonomic balance, such as with aging[38,39], or physical training[38], and in particular under conditions in which heart rate variability is decreased. This may be because the ratio of low to high frequency power is so sensitive to subtle changes in the denominator that a relatively large inter-subject variability arises under these circumstances[39].

A key concept underlying the interpretation of such information concerns the actual mechanism underlying heart rate variability spectral power. Although it has been used by some groups to quantify the intensity of parasympathetic and sympathetic drive to the sino-atrial node, its proper application would appear to be the estimate of the extent to which these branches of the autonomic nervous system are capable of modulating heart rate variability within these particular frequency ranges[26,34,36,40].

Early studies using pharmacological interventions in dogs and humans demonstrated that high frequency components (0.15–0.5 Hz) of physiological heart rate variability are modulated predominately by the parasympathetic nervous system, whereas the lower frequency components (0.05–0.15 Hz) can be modulated by both sympathetic and parasympathetic neural influences[2,3]. In the enthusiasm which followed this work, many studies focused on the effect of different interventions on these spectral components of heart rate variability.
variability and, as a result, the idea evolved, without any direct confirmatory evidence, that spectral components of heart rate variability closely reflect the magnitude of autonomic tone\[41\].

However, this concept is inconsistent with heart rate variability data during exercise in normal subjects where absolute and normalized low frequency spectral power actually decrease during severe exercise, a time when sympathetic activity is known to be high\[42\]. The same pattern can be observed with a pharmacological stimulus to sino-atrial discharge, such as dobutamine\[43\]. Although some authors, using coarse-graining spectral analysis, have reported an appropriate increase in the ratio between low and high frequency spectral power as exercise intensity increases above 60% of peak oxygen uptake, in parallel with increasing catecholamines\[44\], others have found that this ratio does not respond appropriately to autonomic blockade under these conditions\[44\]. Additionally, recent work in the authors’ laboratory has shown that the ratio of low to high frequency spectral power will increase along with MSNA at −15 mmHg of lower body negative pressure in normal humans. However, this ratio reaches a plateau with intense levels of sympathetic activation at higher levels of lower body negative pressure. Consequently, this concordance disappears\[42\]. This is in contrast with the 72% increase in cardiac noradrenaline spillover observed in older normal subjects, under similar experimental conditions\[45\]. It has been proposed that under conditions of receptor saturation or blockade, modulation of autonomic activity is abolished, and the relevant frequency band decreases or disappears\[41\].

This suggests that short-term heart rate fluctuations arise from sino-atrial responsiveness to variations in cardiac autonomic activity, and are not necessarily indicative of mean firing rates of vagal and cardiac sympathetic neural fibres. Unfortunately, some confusion remains in the literature because many studies incorrectly use variability measures for this latter purpose\[27\]. The former approach is also more consistent with the data concerning patients with heart failure, who also exhibit high sympathetic activity and decreased low frequency spectral power of both heart rate variability\[8,10\] (Table 1) and MSNA variability\[12,46\]. Viewed from this perspective, the loss of heart rate spectral power in heart failure can be viewed as evidence for a decrease in modulation of sino-atrial discharge, which may be due to constancy of sympathetic and parasympathetic firing rates or a loss of pacemaker responsiveness to neurally released noradrenaline and acetylcholine.

In summary, whereas studies in normal subjects reveal within-subject changes in the low frequency component of heart rate variability that are concordant with anticipated changes in central sympathetic outflow, the same does not hold for between-subject or group comparisons, particularly during dynamic exercise, or in patients with heart failure. On the whole, power spectra should be considered markers of modulation of neural outflow, rather than of the intensity of this stimulus.

### Table 1 Physical characteristics and spectral power analysis of heart rate variability in heart failure patients and normal subjects. S.E., standard error; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; MSNA, muscle sympathetic nerve activity; SNS, sympathetic nervous system; PNS, parasympathetic nervous system. *P<0·05; †P<0·01; ‡P<0·001

<table>
<thead>
<tr>
<th>(Mean ± S.E.)</th>
<th>Heart failure (n=35)</th>
<th>Normal (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52·4 ± 1·8</td>
<td>47·4 ± 1·8</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>119·5 ± 3·3</td>
<td>121·5 ± 2·5</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72·9 ± 1·8</td>
<td>74·5 ± 1·7</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>72·9 ± 1·8</td>
<td>66·8 ± 1·6</td>
</tr>
<tr>
<td>MSNA (burst.min(^{-1}))</td>
<td>52·9 ± 2·6</td>
<td>34·9 ± 1·9</td>
</tr>
<tr>
<td>Total power (ms(^2))</td>
<td>749·7 ± 166·3†</td>
<td>980·1 ± 127·5</td>
</tr>
<tr>
<td>Harmonic power</td>
<td>172·1 ± 40·1*</td>
<td>286·5 ± 69·4</td>
</tr>
<tr>
<td>Fractal power</td>
<td>577·5 ± 133·5‡</td>
<td>683·6 ± 79·4</td>
</tr>
<tr>
<td>High frequency (&gt;0·15 Hz)</td>
<td>29·6 ± 6·6*</td>
<td>98·8 ± 29·3</td>
</tr>
<tr>
<td>Low frequency (0·0–0·15 Hz)</td>
<td>136·5 ± 36·9</td>
<td>199·0 ± 43·9</td>
</tr>
<tr>
<td>SNS indicator (P(<em>{15}/P</em>{17}))</td>
<td>14·3 ± 5·7</td>
<td>11·6 ± 3·0</td>
</tr>
<tr>
<td>PNS indicator (P(<em>{15}/P</em>{total}))</td>
<td>0·05 ± 0·009</td>
<td>0·1 ± 0·02</td>
</tr>
</tbody>
</table>

### Heart rate variability in heart failure

An accurate non-invasive assessment of cardiac sympathetic activity would be of particular importance in the setting of heart failure due to the association between high sympathetic activity in this condition and both an adverse prognosis\[18,47\] and a decrease in functional capacity\[48,49\]. Sympathetic outflow, as assessed by plasma noradrenaline concentrations and total body noradrenaline spillover, is increased in heart failure\[21,23,24,50–52\]. However, there are quantitative regional differences in sympathetic outflow, particularly in patients with heart failure, with the greatest activation directed at the heart. This was demonstrated by Hasking et al, who showed that while both cardiac and renal noradrenaline spillover are elevated compared with normal subjects, the heart suffers by far the greater increase (5 × vs 2 ×, respectively)\[24\]. As well, Rundqvist et al. reported that the increase in cardiac adrenergic drive, measured by the same technique, precedes any rise in sympathetic nerve traffic to skeletal muscle as measured by microneurography\[23\]. Indeed, cardiac noradrenaline spillover is the best predictor of mortality in advanced heart failure, but requires an invasive catheterization laboratory for its determination\[47\]. An alternate non-invasive method of assessing sympathetic outflow to the heart, such as spectral analysis of heart rate variability, would be highly relevant for this patient population.

However, there are specific limitations to the application of heart rate variability spectra as an estimate of cardiac sympathetic drive in human heart failure. As discussed earlier, these power spectra reflect modulation of neural outflow, rather than the intensity of this stimulus. Second, since cardiac noradrenaline spillover, as measured using the radiotracer technique, is across the left ventricle, and not specific to the sino-atrial node,
it is influenced by a different set of mechanisms. For example, low frequency spectral power is dependent on baroreflex function, cardiac beta-adrenergic receptor sensitivity and post-receptor signal transduction as well as parasympathetic modulation\(^3\), whereas values for cardiac noradrenaline spillover are not affected by postsynaptic mechanisms\(^5\) but can be influenced by any impairment in the efficiency of re-uptake of noradrenaline\(^6\). There is also indirect evidence in humans that stimulation of beta-adrenergic receptors in intrathoracic ganglia and on intrinsic cardiac neurones may contribute to cardiac noradrenaline spillover\(^7\) as has been observed with directly measured cardiac efferent sympathetic nerve activity in dogs\(^8\). Thus, any correlation between heart rate variability estimates of sympathetic activity and cardiac noradrenaline spillover, if present, is likely to be weak especially in heart failure where beta-adrenergic downregulation may be prominent, and post-synaptic beta-adrenergic receptor function may be altered\(^9\).

It should come as no surprise, therefore, to discover disparities between values of low frequency spectral power and other measures of sympathetic activation both in normal subjects\(^10\) and in patients with heart failure\(^11\). Indeed, it is the patients with the greatest increase in MSNA that display the most profound reduction in exercise tolerance, as measured by peak oxygen consumption\(^12\).

Despite these methodological differences, several aspects of heart rate variability have emerged in population studies as independent predictors of early mortality in heart failure or following myocardial infarction. These include a decrease in the slope of spectral exponent \(\beta\)\(^13\), and a decrease in heart rate variability\(^14\). These findings would suggest that the most important application of this methodology in heart failure patients may be in the clinical realm as a means of estimating prognosis. Interestingly, the prognostic value of the low frequency component per se is less clear, given that Ponikowski \textit{et al.}\(^15\) reported an increased risk with a reduced low frequency component, and Szabo \textit{et al.}\(^16\) found that increased low frequency spectral power was associated with increased risk\(^17\). It is possible that differences in disease severity or stage may account for this and other inconsistencies.

Thus, while heart rate variability determination may add to the estimate of prognosis for heart failure patients, this method would appear to have little or no applicability as a means of determining cardiac sympathetic activity in patients with heart failure.

\section*{Time course of changes in heart rate variability in heart failure}

\subsection*{Experimental heart failure}

Studies using a paced canine model of heart failure have found that autonomic imbalance occurs early in the course of ventricular dysfunction, and is accompanied by alterations in heart rate variability. These consist of a progressive decrease in the high frequency spectral component, and an increase in the normalized low frequency spectral power and low to high frequency ratio with worsening heart failure\(^18\). Such changes appear to parallel increases in plasma noradrenaline\(^19\). This temporal concordance would suggest that low frequency power may indeed provide a non-invasive estimate of cardiac sympathetic drive in heart failure.

\subsection*{Human heart failure}

There are no longitudinal studies, of this nature, in human heart failure. Total spectral power has been related to disease severity in functional terms, as assessed by NYHA class\(^20\) (Fig. 1), but with a pattern that differs from that observed in experimental heart failure. These studies are summarized in Table 2.

A predominance of the low frequency component of the heart rate power spectrum has been observed in NYHA class II patients, but this diminishes or becomes absent in class III or IV heart failure. All groups were unresponsive to tilt\(^21\). This pattern is consistent with the concept that early in the course of left ventricular dysfunction, low frequency spectral power is significantly increased, and high frequency power...
### Table 2 Summary of heart rate variability studies characterizing heart failure patients according to severity of disease. NYHA Class, New York Heart Association Classification (I–IV); Tx, cardiac transplantation; nu, normalized units; assoc, associated; asymp, asymptomatic; symp, symptomatic

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of controls</th>
<th>NYHA class</th>
<th>Heart rate variability</th>
<th>Low frequency spectral power</th>
<th>High frequency spectral power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortara et al. 1994[13]</td>
<td>30 pre Tx</td>
<td>15 NYHA 0 or I</td>
<td>III,IV preTx</td>
<td>↓ in 16/30</td>
<td>↑ in 16/30, undetected in</td>
<td>↓ in 16/30 in nu only</td>
</tr>
<tr>
<td></td>
<td>13 post Tx</td>
<td></td>
<td></td>
<td>↓↓ in 14/30</td>
<td>↓↓ in 14/30 assoc with ↓ NYHA</td>
<td>↑ in 16/30 in nu only</td>
</tr>
<tr>
<td>Guzzetti et al. 1995[70]</td>
<td>30</td>
<td>15</td>
<td>II,III,IV</td>
<td>↓↓ in III</td>
<td>↑ in II</td>
<td>↓ in IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 each</td>
<td>↓↓ in IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panina et al. 1996[69]</td>
<td>20</td>
<td>None</td>
<td>II and III</td>
<td>↓ in III vs II</td>
<td></td>
<td>↓ in III–IV vs I–II</td>
</tr>
<tr>
<td>Toepfer et al. 1996[71]</td>
<td>33 male</td>
<td>None</td>
<td>II–IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sculvini et al. 1998[14]</td>
<td>21 asymp</td>
<td>25</td>
<td>0–I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 symp</td>
<td></td>
<td>II–IV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Limitations of spectral analysis of HR variability
Figure 2 Inverse of low frequency power and central sympathetic outflow to muscle in heart failure. In patients with heart failure (n=35), \(1/\log_{10} P_L\) is correlated with muscle sympathetic burst frequency (MSNA) \((r=0.44, P<0.01)\). \(P_L\), low frequency spectral power. From Notarius et al. Clin Sci 1999; 96: 557–65. Reprinted with permission.

Loss of heart rate variability in heart failure

Mechanisms

Various mechanisms have been put forward to account for the loss of heart rate variability in severe heart failure. Loss of modulation of autonomic outflow is consistent with the concept of reduced autonomic modulation at the level of central sympathetic outflow at this frequency component of heart rate variability to estimate cardiac sympathetic activity in humans.

The work of the authors of this review and that of others[12,46] have also documented a loss of low frequency power in the muscle sympathetic nerve activity spectrum itself, despite incessant, pulse-synchronous neural discharge. This would suggest that the loss of modulation of central sympathetic outflow at this specific low frequency becomes an important aspect of the disturbance of neurogenic control of the circulation in heart failure.

In summary, it is the absence, rather than the augmentation, of low frequency power that provides a better estimate of sympathetic drive in heart failure[10]. Rhythmic oscillations in post-ganglionic vagal and sympathetic nerve traffic are fundamental to the generation of heart rate spectral power. The combination of loss of adrenergic modulation and diminished post-ganglionic vagal rhythms in late to end-stage heart failure severely limits the use of the low frequency component of heart rate variability to estimate cardiac sympathetic activity in humans.
advanced heart failure and with high sympathetic nerve traffic.

**Technical concerns**

As patients with congestive heart failure display reduced harmonic power, any attempt to characterize cardiac sympathetic outflow in this condition may be impeded by co-existing non-harmonic (i.e. broadband non-white noise) power within the low frequency range. It is for this reason that the authors’ laboratory has adopted the method of coarse-graining spectral analysis (CGSA). This first identifies and quantifies both the harmonic and non-harmonic components of the power spectrum, and then extracts the non-harmonic component from total power. Extracting this component of the signal avoids overstating the contribution of residual harmonic low frequency spectral power to heart rate variability in heart failure patients.

The need for a standard stimulus, such as timed respiration, standing or tilt, for between-subject comparisons of heart rate variability in patients with heart failure has been raised by some groups. In normal subjects, an increased breathing frequency decreased both low and high frequency spectral power of heart rate variability, whereas in those with heart failure, the response varied according to the severity of disease, as did the response to tilt. Since autonomic neural modulation and cardiovascular responses to neural activity differ at different stages of the disease, the use of stimulation manoeuvres when assessing heart rate variability in patients with heart failure would seem prudent. However, thus far, none of these standardized spectra have been compared with cardiac noradrenaline spillover or other measures of sympathetic nerve activity.

It is important to emphasize that the observations referred to arise from short-term recordings, obtained under standardized laboratory conditions. It is anticipated that any limitations on the interpretation of information acquired under such near-ideal conditions will be further amplified by the analysis of longer-term, i.e. 24-h ambulatory heart rate, recordings which compromise essential technical considerations, such as stationarity.

**Very low frequency oscillations of HRV**

Altered breathing patterns, as may be seen in Cheyne Stokes respiration, shift spectral power into the very low frequency range (<0.05 Hz) in patients with moderate to severe heart failure. Although the underlying mechanism remains unclear, spectral power in this band may indicate enhanced peripheral chemoreceptor sensitivity. An increase in very low frequency spectra in heart failure may also be associated with an increased mortality risk, but it is not known whether or how this might relate to changes in cardiac sympathetic activity.

Therefore, loss of heart rate modulation, technical considerations and alteration in breathing patterns act to limit the utility of heart rate variability indices as estimates of cardiac autonomic activity.

**Effect of interventions on heart rate variability in heart failure**

Both pharmacological and non-pharmacological interventions can enhance heart rate variability in heart failure.

**Pharmacological interventions**

Angiotensin converting enzyme inhibition with enalapril has been shown to increase spectral power across all frequencies in heart failure subjects. These changes correlated with reductions in plasma angiotensin II levels. In another study, low doses of captopril increased time domain estimates of parasympathetic nervous activity in heart failure patients. Similar improvements have been reported with central sympathetic inhibition with clonidine and with long-term beta-blockade. Digitalis has also been shown to increase vagal activity, and partly restore the disturbed circadian rhythm of heart rate variability.

**Non-pharmacological interventions**

Total and high frequency spectral power increase with aerobic exercise training. Continuous positive airway pressure, which may have mortality benefits in heart failure patients with Cheyne Stokes respiration, increased total spectral power, non-harmonic power, low and high frequency power and the ratio of high to total power when applied to patients with heart failure. After cardiac transplantation, low frequency MSNA variability significantly increased whereas spectral components of heart rate variability were unchanged. A positive relationship between total power of heart rate variability and time post-transplant suggests the possibility of cardiac re-innervation in some subjects.

These observations are consistent with the known effect of these pharmacological and non-pharmacological interventions on the autonomic disturbances associated with heart failure. This would suggest that while there is limited use for sympathetic indices of heart rate variability at rest, they may reflect changes in autonomic balance within individuals following a particular intervention. However, there is a need for long-term studies to determine whether these improvements per se impact positively on prognosis.
Conclusions

In summary, so-called sympathetic contributions to heart rate variability are more indicative of the strength of modulation of autonomic outflow than the intensity of cardiac sympathetic nerve traffic, particularly in pathological conditions such as congestive heart failure. They do not correlate with other measures of regional or global sympathetic outflow at rest in heart failure, and any concordance reported appears to vary with the severity of disease. Therefore, when considered in the context of previous work, frequency domain measures of heart rate variability, obtained under resting conditions, should not be used to derive inferences as to differences in central or cardiac sympathetic outflow in individual heart failure subjects. Two promising applications of this method in heart failure are the identification of patients at high risk of adverse events and assessment of the impact of pharmacological and non-pharmacological interventions within individual patients.

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